Clinical study for management of supportive treatment for high-dose chemotherapy with peripheral blood stem cell transplantation (PBSCT) for intractable testicular tumor

AUTHOR(S):

Shigemura, Katsumi; Tanaka, Kazushi; Hara, Isao; Muramaki, Mototsugu; Arakawa, Soichi; Fujisawa, Masato

CITATION:

Shigemura, Katsumi ...[et al]. Clinical study for management of supportive treatment for high-dose chemotherapy with peripheral blood stem cell transplantation (PBSCT) for intractable testicular tumor. 泌尿器科紀要 2006, 52(7): 531-536

ISSUE DATE:

2006-07

URL:

http://hdl.handle.net/2433/71191

CLINICAL STUDY FOR MANAGEMENT OF SUPPORTIVE TREATMENT FOR HIGH-DOSE CHEMOTHERAPY WITH PERIPHERAL BLOOD STEM CELL TRANSPLANTATION (PBSCT) FOR INTRACTABLE TESTICULAR TUMOR

Katsumi Shigemura, Kazushi Tanaka, Isao Hara, Mototsugu Muramaki, Soichi Arakawa and Masato Fujisawa

The Division of Urology, Department of Organs Therapeutics, Faculty of Medicine, Kobe University Graduate School of Medicine

The side effects of high-dose anti-cancer drug chemotherapy with peripheral blood stem cell transplantation (PBCST) for the treatment of intractable testicular tumor are very serious. In particular, agranulocytosis in bone marrow suppression may be life threatening. In this study, we examined opportunistic infectious diseases and preventive counter measures in the compromised conditions of anti-cancer drug chemotherapy. The patients underwent anti-cancer drug chemotherapy with PBCST for the treatment of intractable testicular tumors at Kobe University Hospital from September 1996 to September 2002. The high-dose chemotherapy regimen consisted of total doses per course of 1,250 mg/m^2 carboplatin, 1,500 mg/m^2 etoposide, and 7,500 mg/m^2 ifosfamide.

Twenty-four men (median age, 30 years ; range, 18–70 years) received 50 courses of chemotherapy in total. The nadir of peripheral leukocyte counts was less than 1,000/mm^3 in all courses, and the mean period was for 7.1 days. None of these patients developed critical sepsis leading to disseminated intravascular coagulation or treatment-related death. Our detailed data show that we can perform high-dose anti-cancer drug chemotherapy with PBSCT for intractable testicular tumors without serious infectious complications if we take sufficient preventive countermeasures for infectious diseases.

(Hinyokika Kiyo **52**：531-536, 2006)

Key words：Supportive care, High-dose chemotherapy, Testicular tumor

INTRODUCTION

Intractable testicular tumors are increasingly treated by anti-cancer chemotherapy and this treatment has given patients better prognosis. Especially in the second line chemotherapy against this tumor, new regimens have been reported. One new regimen, high-dose anti-cancer chemotherapy with carboplatin, etoposide and ifosfamide, is often used together with peripheral blood stem cell transplantation (PBSCT). A much larger quantity of anti-cancer agents is given to patients in this regimen because most of the patients are younger than 40 years old and have good performance control. The regimen often has three or four courses of anti-cancer chemotherapy and therefore the period of taking medication becomes longer. In addition, most of the patients have this regimen just after the first line regimen such as BEP therapy (bleomycin, etoposide, and cisplatin) for intractable testicular cancer, which may already have caused side effects. There are often various side effects from anti-cancer chemotherapy and they may be serious. PBSCT has been frequently applied to bone marrow rescue, because of its low invasiveness and early hematologic recovery compared with bone marrow transplantation after high-dose anti-cancer chemotherapy[1-5].

Patients have been reported to die from the side effects of anti-cancer chemotherapy[2,6]. Transient or permanent renal dysfunction is a major side effect and several measures such as hydration are often taken to prevent it[7]. Especially in the suppression of bone marrow function, a decrease of granulocytes often brings about an immunosuppressive status for patients. Patients sometimes have severe pneumonia or sepsis that may lead to death. Bacterial, viral, and fungal infections originate in patients especially during the period of treatment with anti-cancer drugs because these patients are considered to be compromised hosts. Few papers have focused on preventive measures against the side effects such as infectious diseases. Therefore, we have to consider not only how to use antibiotics, anti-viral, and anti-fungal agents, but also how to take care of bone marrow function.

In this study, we investigated various opportunistic infections with detailed data analysis as a side effect of taking high-dose anti-cancer chemotherapy and the measures for preventing severe infections.

METHODS

Patients

This study was performed on 24 men who underwent 50 courses of high-dose anti-cancer drug chemotherapy with PBSCT as the second or third line chemotherapy for the treatment of intractable testicular tumors at the urology ward of Kobe University Hospital from September 1996 to September 2002. We followed the criteria of Nakagawa et al regarding patients' selections[8].

Anti-cancer chemotherapy regimen

Daily doses of 250 mg/m^2 carboplatin, 300 mg/m^2 etoposide and 1,500 mg/m^2 ifosfamide were administered intravenously for five consecutive days. Thus in one course of chemotherapy, the patient received a total dose of 1,250 mg/m^2 carboplatin, 1,500 mg/m^2 etoposide, and 7,500 mg/m^2 ifosfamide. A period of 28 days was considered to be one course and the patient underwent one to four courses.

Peripheral blood stem cell transplantation (PBSCT)

Peripheral blood stem cells were collected during bone marrow regeneration after conventional first line therapy such as BEP (bleomycin, etoposide, and cisplatin) regimen. We previously reported the efficacy of BEP therapy for the mobilization of peripheral blood stem cells in patients with germ cell cancer[9,10]. Briefly, recombinant human granulocyte colony stimulating factor (rhG-CSF) was administered from the day when the leukocyte count in the peripheral blood decreased below 2,000/μl and was continued until the peripheral blood stem cells were harvested. Leukoapheresis was performed once or twice during each cycle of chemotherapy. Peripheral blood stem cells were collected by means of leukoapheresis, using a Cobe Spectra continuous flow cell separator (Cobe Laboratories, Lakewood, Colorado, USA), when leukocyte and platelet counts in the peripheral blood reached at least 10,000 and 50,000/μl, respectively. Cryopreservation in liquid nitrogen, thawing, and transfusion proceeded according to standard procedures. Peripheral blood stem cells were transplanted 72 h after the last administration of chemotherapeutic agents. Haptoglobin was administered over 2 h before PBSCT to prevent renal dysfunction due to hemolysis.

Measures for preventing infection

The patients began wearing a mask and gargling with povidone iodine from Day 0 of the high-dose anti-chemotherapy course; on Day 7, we moved the patients to individual rooms and the patients started taking oral vancomycin (1.5 g) and amphotericin B (12 ml), inhaling amphotericin B and tobramycin, and taking intravenous fluconazole (100 mg). On Day 8, the patients underwent PBSCT and on Day 9, we started injecting granulocyte colony stimulating factor (G-CSF) 300 μg a day subcutaneously to patients every day until the number of peripheral leukocytes exceeded 10,000/mm^3)[3]. Patients with a high-grade fever of more than 38°C underwent immediate culture testing and received γ-globulin and meropenem intravenously as a rule. We investigated peripheral leukocyte counts, fever duration, and isolated bacteria.

RESULTS

Twenty-four patients had an average age of 36.2 years (range, 18－70 years; median age, 30 years). The histology of the tumors was mostly non-seminoma, and the cancer was mostly classified to stage IIIA or IIIB2 or IIIC according to Staging Classification of the Japanese Urological Association. In our cases, 6 patients were classified into the good prognosis group, 6 into the intermediate prognosis group, and 11 into the poor prognosis group according to the International Germ Cell Cancer Collaborative Group (IGCCCG) risk criteria (one patient was unknown.)[11].

As a first line anti-cancer chemotherapy regimen, BEP (cisplatin, etoposide, and bleomycin) was the most often used. Of the 21 patients who underwent BEP as the first line chemotherapy, most patients underwent more than 2 courses. Regarding the data of infectious complication, of the 50 courses, 44 (88%) had a nadir of peripheral leukocyte counts of less than 500/mm^3 for a mean period of 5.0 days. Patients in 44 courses (88%) had a fever greater than 38°C. The periods of having high-grade fever nearly correlated to the period when bone marrow suppression was most serious and the high fever tended to subside as the peripheral white blood cell count rose. In 3 courses (6%), blood bacterial culture tests were positive. The isolated bacteria in the blood culture tests were *Bacillus* spp., methicillin-resistant *Staphylococcus aureus* (MRSA), and *Staphylococcus epidermidis*.

We cured all three cases with positive blood culture tests. The first case (isolated bacteria: *Bacillus* spp.) was in a 45-year-old with stage IIIC. He had received 2 courses of BEP as the first-line chemotherapy, and developed bacteremia in the first cycle of high-dose chemotherapy. His body temperature was 37－38°C, and his WBC nadir was 100/mm^3. Treatment with meropenem was started when his body temperature rose above 38°C. He was successfully cured judging from the data of WBC count. The second case (isolated bacteria: *S. epidermidis*) was in a 31-year-old with stage IIIC. He had received 3 courses of BEP as the first-line chemotherapy, and developed bacteremia in the third cycle of high-dose chemotherapy. His body temperature was 38－40°C, and his WBC nadir was 0/mm^3. He received the treatment with imipenem/cilastatin when his body temperature rose above 38°C. He was successfully cured judging from the data of WBC count. The third case (isolated bacteria: MRSA) was in a 21-year-old with stage IIIB2. He had received 3 courses of BEP as the first-line chemotherapy, and developed bacteremia in the first cycle of high-dose chemotherapy. His body temperature was 38－40°C, and his WBC nadir was 200/mm^3. He underwent the treatment with meropenem when his body temperature rose above 38°C, and after his blood culture result

Table 1. Patient background, tumor histology and staging, risk criteria, and 1st line chemotherapy

Number (patients)		24
Courses		50
Age	Range	18–70
	Average	36.2
	Median	30
Histology (%)	Seminoma	2 (8.3)
	Mixed type (Including Seminoma)	7 (29.2)
	Non-Seminoma	10 (40)
	Mixed type	5
	Teratoma	1
	Choriocarcinoma	2
	Yolk Sac Carcinoma	1
	Embryonal Carcinoma	1
	Necrosis	1 (4.2)
	Unconfirmed	4 (16.7)
Clinical Stage (%)	I	2 (8.3)
	IIA	1 (4.2)
	IIB	5 (20.8)
	IIIA	2 (8.3)
	IIIB2	8 (33.3)
	IIIC	5 (20.8)
	Extragonadal	1 (4.2)
Risk criteria classification*	Good	6 (25)
	Intermediate	6 (25)
	Poor	11 (45.8)
	Unknown	1 (4.2)
1st line regimen**	BEP	21
	4 courses	1
	3 courses	9
	2 courses	8
	Unknown	3
	VIP	2
	Unknown	1

* Classified according to International germ cell cancer collaborative group (IGCCCG) risk criteria. ** BEP : Bleomycin, Etoposide, and Cisplatin ; VIP : Etoposide, Ifosfamide, and Cisplatin.

Table 2. Patients' data relating to side effects

Courses (%) when plasma WBC is less than 1,000/mm^3	50 (100)
Courses (%) when plasma WBC is less than 500/mm^3	44 (88)
Average periods (days) when plasma WBC is less than 1,000/mm^3	7.1
Average periods (days) when plasma WBC is less than 500/mm^3	5
Courses (%) when patients have high grade fever (above 38°C)	44 (88)
Courses (%) when patients have high grade fever (above 39°C)	22 (44)
Courses (%) when patients have high grade fever (above 40°C)	5 (10)
Courses (%) when patients have positive culture tests	8 (16)
Courses (%) when patients have positive blood culture tests	4 (8)
Isolated bacteria in blood culture tests	*Baccilus* spp., MRSA*, *Staphylococcus epidermidis*

* MRSA : methicillin resistant *Staphylococcus aureus*.

became MRSA-positive, we immediately exchanged the central venous catheter and changed antimicrobial medication to vancomycin, and then he was successfully cured (Tables 1 and 2).

DISCUSSION

The second line chemotherapy against intractable testicular tumors has been frequently discussed. Motzer et al.[10] reported high-dose anti-cancer chemotherapy with PBSCT, which has been a valuable tool for treating intractable testicular tumors. Currently, high-dose chemotherapy is recommended with intensification of treatment for patients with advanced disease and poor prognosis in the latest guideline on testicular cancer[12].

Therefore, many institutions have selected this method and regimen after the first-line chemotherapy in which cisplatin is included. In the regimen of high-dose anti-cancer chemotherapy with PBSCT, the doses of anti-cancer reagents used should be carefully chosen to be potent without serious side effects. We examined the infections in these compromised hosts by granulocyte reduction resulting from bone marrow suppression as a serious side effect and the supportive measures for preventing serious infections. Among these side effects, agranulocytosis in bone marrow suppression may be life threatening. Many authors have stated that this anti-cancer chemotherapy is a valuable method for the second line chemotherapy treatment of intractable testicular tumors.

High-dose chemotherapy treatment was established by Nichols et al. who reported a 13% rate of treatment-related death in 1992[2] and Siegert et al. reported two treatment-related deaths out of 74 patients in earlier studies[9]. Recently, Motzer et al. reported the efficacy and safety of high-dose chemotherapy as the first-line strategy for patients with poor risk germ-cell tumors[7]. However, there have been very few reports focusing on the measures for the prevention and control of infections or various other side effects, and to discuss the kinds of supportive care with detailed data analysis in high-dose anti-cancer chemotherapy as the second line in which the patients already had potentially severe bone marrow function suppression. Therefore, we focused on the data regarding infectious complications considered to be useful, especially for establishing new anti-cancer chemotherapy regimens and supportive care managements on any kind of anti-cancer drug chemotherapy. As supportive therapies improved, the rate of treatment-related deaths in high-dose chemotherapy decreased. As a result, the rate of treatment-related deaths has recently dropped to less than 4%[7].

None of our patients died from the side effects of high-dose chemotherapy. We also had no serious cases of sepsis in the periods of anti-cancer chemotherapy and no definite trends of isolated bacteria from culture tests. We successfully cured all bacteremia cases, and isolated MRSA in one case. We could treat him successfully and appropriately by following the results of a blood culture test properly. From this experience, we strongly recommend culture tests.

Additionally, our data regarding the periods of low leukocyte count (less than 500/mm^3) and the frequencies of febrile side effects revealed that the side effects caused by bone marrow suppression are so serious that we should pay more attention to patient care and react quickly when patients have febrile side effects. Regarding antibiotics prophylactic medication, Infectious Diseases Society of America (IDSA) and Center for Diseases Control (CDC) guidelines do not necessarily recommend it routinely because of limited data, but they have recommended some drugs including anti-fungal drugs. In addition, they stated that using prophylactic antibiotics might reduce bacteremia rates after hematopoietic stem cell transplant (HSCT) but infection-related fatality rates are not reduced, and if physicians choose to use prophylactic antibiotics, they should routinely review hospital and HSCT center antibiotic-susceptibility profiles[13,14]. From these points of view, we need not only to select cases and reconsider the prophylactic drug, but also to continue performing culture tests.

As IDSA guideline reported[13], Masaoka stated that for high-risk patients with neutropenic fever, monotherapy (cefepime or ceftazidime or carbapenem) or combination therapy (cefepime or ceftazidime or carbapenem＋aminoglycoside) is recommended[15]. In addition he mentioned that the therapy with γ-globulin is not recommended for routine use but can be considered for patients with persistent febrile neutropenia and a predictably worsening clinical course. Therefore, we have to consider the next task to select the patients who need to be treated with γ-globulin and those who do not for their clinical courses.

CONCLUSION

None of our 24 patients developed critical sepsis leading to disseminated intravascular coagulation, multiple organ failure, or treatment-related death after receiving 50 courses of high-dose anticancer chemotherapy with PBSCT as the second line for their intractable testicular tumor. Our detailed data show that we can perform this regimen without serious infectious complication if we perform sufficient preventive countermeasures for infectious disease caused as side effect.

REFERENCES

1) Motzer RJ, Mazumdar M, Bosl GJ, et al.: High-dose carboplatin, etoposide, and cyclophosphamide for patients with refractory germ cell tumors: treatment results and prognostic factors for survival and toxicity. J Clin Oncol **14**: 1098–1105, 1996
2) Nichols CR, Andersen J, Lazarus HM, et al.: High-dose carboplatin and etoposide with autologous

bone marrow transplantation in refractory germ cell cancer : an Eastern Cooperative Oncology Group protocol. J Clin Oncol **10** : 558–563, 1992
3) Motzer RJ, Gulati SC, Crown JP, et al. : High-dose chemotherapy and autologous bone marrow rescue for patients with refractory germ cell tumors : early intervention is better tolerated. Cancer **69** : 550–556, 1992
4) Bokemeyer C and Schmoll HJ : Treatment of advanced germ cell tumours by dose intensified chemotherapy with haematopoietic growth factors or peripheral blood stem cells (PBSC). Eur Urol **23** : 223–230, 1993
5) Henon PR, Liang H, Beck-Wirth G, et al. : Comparison of hematopoietic and immune recovery after autologous bone marrow or blood stem cell transplants. Bone Marrow Transpl **9** : 285–291, 1992
6) Siegert W, Beyer J, Strohscheer I, et al. : High-dose treatment with carboplatin, etoposide, and ifosfamide followed by autologous stem-cell transplantation in relapsed or refractory germ cell cancer : a phase I/II study. The German Testicular Cancer Cooperative Study Group. J Clin Oncol **12** : 1223–1231, 1994
7) Motzer RJ, Mazumdar M, Bajorin DF, et al. : High-dose carboplatin, etoposide, and cyclophosphamide with autologous bone marrow transplantation in first-line therapy for patients with poor-risk germ cell tumors. J Clin Oncol **15** : 2546–2552, 1997
8) Nakagawa S, Miki T, Akaza H, et al. : High-dose chemotherapy with peripheral blood stem cell autotransplantation for patients with poor-risk testicular germ cell tumors--pilot study of the Japan Blood Cell Transplantation Study Group. Hinyokika Kiyo **45** : 805–809, 1999
9) Yamada Y, Hara I, Gohji K, et al. : Recovery of leukocyte function after super-high-dose chemotherapy with peripheral blood stem cell transplantation in testicular cancer patients. Int J Cancer **72** : 39–42, 1997
10) Hara I, Yamada Y, Miyake H, et al. : Clinical outcome of high-dose chemotherapy combined with peripheral blood stem cell transplantation for male germ cell tumors. Anti-cancer Drug **10** : 711–718, 1999
11) International Germ Cell Consensus Classification : a prognostic factor-based staging system for metastatic germ cell cancers. International Germ Cell Cancer Collaborative Group. J Clin Oncol **15** : 594–603, 1997
12) Albers P, Albrecht W, Algaba F, et al. : Guidelines on testicular cancer. Eur Urol **48** : 885–894, 2005
13) Hughes WT, Armstrong D, Bodey GP, et al. : 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. Clin Infect Dis **15** : 730–751, 2002
14) Guideline for preventing Opportunistic Infections Among Hematopoitic Stem Cell Transplant Recipients (Recommendations of CDC, the Infectious Diseases Society of America, and the American Society of Blood and Marrow Transplantation) CDC Morb Mortal Wkly Rep **49** : RR–10, 2000
15) Masaoka T : Evidence-based recommendations for antimicrobial use in febrile neutropenia in Japan : excutive summary. Clin Infect Dis **39** : S49–52, 2004

(Received on September 22, 2005
Accepted on February 11, 2006)

和文抄録

難治性精巣腫瘍に対する末梢血幹細胞移植併用大量抗癌化学療法時の感染予防に関する検討

重村　克巳，田中　一志，原　　勲
村蒔　基次，荒川　創一，藤澤　正人
神戸大学大学院医学系研究科器官治療医学講座腎泌尿器科学分野

難治性精巣腫瘍に対する末梢血幹細胞移植併用大量抗癌化学療法の副作用はとても重篤である．とくに骨髄抑制における無顆粒球症は時に患者を死に至らしめることもある．今回われわれは抗癌剤投与による免疫力低下状態における日和見感染症とその予防策について検討した．

対象は1996年9月から2002年9月までの期間に神戸大学医学部付属病院において難治性精巣腫瘍にて末梢血幹細胞移植併用大量抗癌化学療法を施行した患者である．大量抗癌化学療法の regimen は total dose で1コースあたり 1, 250 mg/m^2 carboplatin，1, 500 mg/m^2 etoposide，7, 500 mg/m^2 ifosfamide を用いた．

計24人，のべ50コースの当療法が行われ，患者の年齢は中間値30歳，範囲は18歳から70歳であった．全50コースにおいて，末梢白血球数の nadir は 1, 000/mm^3 以下となり，その平均期間は7. 1日間であった．播種性血管内凝固を起こした重篤敗血症症例や治療関連死は認めなかった．

当データにより難治性精巣腫瘍に対する末梢血幹細胞移植併用大量抗癌化学療法は十分な感染症に対する予防策がとられれば，重篤な感染性合併症なく施行しうることが示された．

（泌尿紀要 **52**：531-536，2006）